Endocrinol Nutr. 2016;63(2):87–94

ENDOCRINOLOGÍA Y NUTRICIÓN

www.elsevier.es/endo

REVIEW ARTICLE

Calcitriol-modulated human antibiotics: New pathophysiological aspects of vitamin D☆

Carlos Antonio Amado Diago[a,*], **María Teresa García-Unzueta**[b], **María del Carmen Fariñas**[c], **Jose Antonio Amado**[d]

[a] *Servicio de Neumología, Hospital Universitario Marqués de Valdecilla, IDIVAL, Universidad de Cantabria, Santander, Spain*
[b] *Servicio de Bioquímica Clínica, Hospital Universitario Marqués de Valdecilla, IDIVAL, Universidad de Cantabria, Santander, Spain*
[c] *Servicio de Enfermedades Infecciosas, Hospital Universitario Marqués de Valdecilla, IDIVAL, Universidad de Cantabria, Santander, Spain*
[d] *Servicio de Endocrinología y Nutrición, Hospital Universitario Marqués de Valdecilla, IDIVAL, Universidad de Cantabria, Santander, Spain*

Received 20 May 2015; accepted 7 September 2015
Available online 9 March 2016

KEYWORDS
Cathelicidin;
Defensin;
Hepcidin;
Calcitriol;
Vitamin D

Abstract Traditionally, calcitriol has been considered a calcium and phosphate regulating hormone, but has recently been shown to play a pivotal role in innate immunity. Many barrier and immune cells have membrane and intracellular receptors that recognize different microbial antigens. Activation of these receptors induces synthesis of 1α-hydroxylase, which acts on 25 hydroxyvitamin D to generate intracellular calcitriol. Calcitriol activates its receptor and enhances the synthesis of important human antibiotics like cathelicidin and β2-defensin while inhibiting hepcidin. These pluripotent peptides have an important role in innate immunity, and their regulation is abnormal in hypovitaminosis D. The literature on their secretion mechanisms, levels in different organic fluids, mechanism of action, and relationship with vitamin D is reviewed here.

PALABRAS CLAVE
Catelicidina;
Defensina;
Hepcidina;
Calcitriol;
Vitamina D

Antibióticos humanos modulados por calcitriol: nuevos aspectos fisiopatológicos de la hipovitaminosis D

Resumen El calcitriol ha sido considerado durante años exclusivamente como una hormona reguladora del metabolismo fosfocálcico, pero últimamente se ha demostrado que numerosas células implicadas en la inmunidad innata (epitelios de barrera, monocitos/macrófagos, etc.)

☆ Please cite this article as: Amado Diago CA, García-Unzueta MT, Fariñas MC, Amado JA. Antibióticos humanos modulados por calcitriol: nuevos aspectos fisiopatológicos de la hipovitaminosis D. Endocrinol Nutr. 2016;63:87–94.

* Corresponding author.
E-mail address: camado@humv.es (C.A. Amado Diago).

son capaces de reconocer determinadas moléculas repetitivas características de diversos gérmenes patógenos mediante receptores de membrana o intranucleares. La activación de estos receptores induce la síntesis de la 1α-hidroxilasa, con lo que dichas células son capaces de sintetizar calcitriol a partir de la 25 hidroxivitamina D circulante. El calcitriol, a través del receptor la vitamina D, modula la expresión de determinados péptidos antimicrobianos, como la catelicidina, la β2-defensina o la hepcidina. Estos péptidos representan un mecanismo versátil de la lucha antibacteriana innata y su producción se ve alterada en la hipovitaminosis D. Se realiza un análisis de la literatura sobre sus mecanismos de secreción, las concentraciones en diversos líquidos orgánicos, y los mecanismos de acción y su relación con la vitamina D.

Introduction

Humans obtain vitamin D or calciferol from diet (in a small proportion) and, primarily, from endogenous synthesis in the epidermis through the effect of ultraviolet radiation.[1] To be active, calciferol should be hydroxylated twice, first at position 25 and then at position 1α, to be converted into 1α,25-dihydroxycalciferol or calcitriol, which behaves at systemic (endocrine) level as an essential hormone for phosphorus and calcium metabolism, and at local (autocrine or intracrine) level as a substance regulating multiple cell functions independent of calcium metabolism.

Calciferol is initially hydroxylated in the liver through the effect of 25-hydroxylase of microsomal CYP2R1.[2] This enzyme is poorly regulated, and massive, direct conversion of the calciferol that reaches the liver into 25-hydroxycalciferol therefore occurs. This is bound to vitamin D binding protein and has a long half life. Thus, its plasma levels are the main indicator of the nutritional status of vitamin D.

The second hydroxylation may occur in the kidney (classical hormonal pathway) or in other cells unrelated to phosphorus and calcium metabolism (nonclassical intracrine or paracrine pathways)[2] through 1α-hydroxylase (CYP27B1) which generates the active metabolite. This enzyme, unlike 25-hydroxylase, is strongly regulated, but regulation at kidney level and at other cells is different. PTH and other factors activate the enzyme in the kidney, while phosphate and fibroblast growth factor 23 (FGF23) are negative regulators.[2]

Calcitriol exerts its regulatory effects mainly, but not only, through activation of its receptor (VDR).[3] VDR is a nuclear receptor which has both a carboxy-terminal portion that binds calcitriol, and an amino-terminal portion that binds to DNA. Calcitriol binding to VDR induces heterodimerization with the X receptor activated by retinoic acid. This is bound to specific DNA sequence elements (VDRE) in the promoter region of genes that will respond to vitamin D. Finally, a molecular complex is assembled that induces or represses gene transcription, thus modulating the synthesis of many proteins.[3]

The presence of nonclassical effects (independent of calcium and phosphorus metabolism) of calcitriol is based on: (1) a demonstration of 1α-hydroxylase activity in multiple extrarenal cells, regulated by their own mechanisms (Table 1); (2) the presence of VDR in multiple cells (it is estimated that up to 3% of the human genome is modulated by calcitriol) (Table 2); and (3) the existence of specific effects mediated by VDR activation in these cells.[4–6] This is a very primitive pathway from the evolutionary point of view, prior to the hormone pathway. The effect of vitamin D and its deficiency on calcitriol-modulated human antibiotics is reviewed below.

Table 1 Tissues with extrarenal expression of 1α-hydroxylase and calcitriol production.

Monocytes/macrophages	Dendritic cells
Endothelial cells	Bronchial epithelium
Pleural mesothelial cells	Brain
Breast	Pancreatic islets
Parathyroid glands	Skin (keratinocytes)
Prostate	Colon
Myoblasts, regenerating skeletal muscle	
Placenta (fetal trophoblasts, maternal decidual cells)	

Antibacterial effects of vitamin D

The association of rickets and infection has a long history. In the 19th century, the use of cod liver oil (an excellent source of vitamins A and D) was recommended not only for treating rickets, but also for pulmonary tuberculosis, and, a little later, sanatoriums specializing in heliotherapy under natural sunlight became fashionable. In 1903, Niels Finsen was awarded the Nobel Prize for Medicine for his work showing that ultraviolet light could cure tuberculosis of the skin.

In 1981, Barbour et al. showed extrarenal calcitriol production in sarcoidotic granulomas in an anephric patient with hypercalcemia.[7] Calcitriol was later shown to promote the fusion of alveolar mouse macrophages.[8] This was the first evidence of the effect of calcitriol on immune system cells. In 1983, Proveddini et al. found VDR in human WBCs.[9] In 1986, vitamin D and interferon-γ were shown to be able to control the proliferation of Mycobacterium tuberculosis in human monocytes.[10]

Wang et al. showed that calcitriol induced the expression of two human antimicrobial peptides, cathelicidin and